REMARKS

This response addresses the rejections raised in both the instant office action and the office action mailed August 25, 2005. In the office action mailed August 25, 2005, the Examiner rejected claims 13-17, 20-25, and 48-51 but indicated that claims 2, 4-12, and 26-30 were allowable. In response, applicants canceled rejected claims 13-17, 20-25, and 48-51 to facilitate the issuance of the then-allowed claims (see Applicant's Amendment After Final received by the Office on October 17, 2005). In the instant office action, the Examiner withdrew the allowability of claims 2 and 4-11 and rejected these claims based on newly discovered references. Under this circumstance, applicants choose to address the rejections against claims 2 and 4-11 raised in the instant office action (Part I below) as well as the rejections against canceled claims 13-17, 20-25, and 48-51 raised in the office action of August 25, 2005 (Part II below). The above canceled claims are now presented as new claims 52-66. New claims 52-56, 62, and 63-66 are the same as canceled claims 13-17, 25, and 48-51, respectively. New claims 57-61 correspond to but differ from canceled claims 20-24, respectively, due to amendments introduced for clarity purposes, which will become clear in connection with the discussions provided in Part II, sections 2 and 3.

In view of the amendments noted above and the remarks below, the applicants respectfully request reconsideration of the merits of this patent application.

No extension of time is believed to be necessary and no fee is believed to be due in connection with this response. However, if any extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to Deposit Account No. 17-0055. No other fee is believed to be due in connection with this response. However, if any fee is due in this or any subsequent response, please charge the fee to the same Deposit Account No. 17-0055.

PART I. RESPONSE TO REJECTIONS RAISED IN THE INSTANT OFFICE ACTION

In the instant office action, the Examiner rejected claims 2, 4-6, 8, and 9 under 35 U.S.C. §102(b) as being anticipated by Labrenz et al. (Science 290:1744-1747, 2000) or Lou et al. (Clinical Chemistry 39:619-624, 1993). Claims 7 and 10-12 are indicated to be allowable if rewritten in independent form. Claims 26-30 are indicated to be allowable.

1. Rejection based on Labrenz et al.

In making the anticipation rejection based on Labrenz et al., the Examiner first alleged that the description provided in the specification in connection with the size of Se(0) particles is general in nature and the specification does not indicate an actual measurement of the Se(0) particles. The Examiner asserts that claims 2, 4-6, 8, and 9 can be anticipated by a composition comprising elemental Se and/or a colloidal Se. Applicants respectfully disagree and note that according to the Federal Circuit, "[a]nticipation requires the disclosure in a single prior art reference each element of the claim under consideration" (*see, e.g.,* W.L. Gore & Assocs. V. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983)). The claims at issue, as amended, specifically recite (directly or indirectly) Se(0) particles with diameters of 0.4 to 5 nanometers and 0.4 to 1 nanometer. As a result, they can only be anticipated by a reference that specifically discloses Se(0) particles of the above sizes, provided that other claim limitations are also disclosed in the same reference.

With respect to the reference itself, the Examiner asserts that Labrenz et al. disclosed micrometer-scale, spherical aggregates of 2- to 5-nanometer (e.g., ~3-nanometer) diameter sphalerite (ZnS) particles formed within natural biofilms of sulfate-reducing bacteria and said biofilms were collected from a flooded tunnel within carbonate rocks wherein the water meets drinking standards. The Examiner further asserts that the reference disclosed that said ZnS contains Se. The Examiner thereby concluded that claims 2, 4-6, 8, and 9 are anticipated. Applicants respectfully disagree.

First of all, Labrenz et al. did not specify that the minor contaminant Se in the ZnS particles is in the oxidation state of zero (zero-valence). Applicants note that in Table 2 of Labrenz et al. wherein the minor contaminants in the ZnS particles are listed, the column for the contaminants, including Se, is labeled "ion." As claims 2, 4-6, 8, and 9 specifically recite zero-valence Se (Se(0)), these claims are not anticipated by Labrenz et al.

Secondly, Labrenz et al. did not disclose a pharmaceutically acceptable delivering medium in connection with the Se contaminant. The Se disclosed in Labrenz et al. is associated with ZnS particles, not the water that meets the drinking standards. According to Labrenz et al., ZnS particles are precipitated in the biofilm of sulfate-reducing bacteria (*see, e.g.,* Labrenz et al., page 1747, left column, lines 1-2) and therefore they are not in the water. Labrenz et al.

provided that the reason why the water meets drinking standards is because Zn and probably As and Se were stripped from the water in the form of ZnS precipitates (see Labrenz et al., the paragraph bridging pages 1746 and 1747). Labrenz et al. estimated that the biofilm has concentrated Zn at least 10^6 times relative to the bulk fluid (i.e., water; see Labrenz et al., the paragraph bridging pages 1746 and 1747 at page 1747). Therefore, it is clear that the Se contaminant is associated with ZnS, which is in turn associated with a film of sulfate-reducing bacteria. The amount of ZnS associated with the Se contaminant is more than 23,000 times of that of Se by weight (in Table 2 of Labrenz et al., the Se contaminant is listed as 0.0042% of ZnS by weight). Such an overwhelming amount of ZnS (which is in turn associated with a film composed of sulfate-reducing bacteria) would be toxic and certainly cannot be considered a pharmaceutically acceptable delivering medium. As claims 2, 4-6, 8, and 9 specifically recite a pharmaceutically acceptable delivering medium, these claims are not anticipated by Labrenz et al. further for this reason.

Thirdly, the particles disclosed by Labrenz et al. are not Se(0) particles but particles of "ZnS + some minor contaminants," including Se of unspecified ionic state (Table 2). There is no disclosure on the aggregation state or the size of the Se contaminant. Although the size of the "ZnS + contaminants" particles is disclosed to be 2 to 5 nanometers and the amount of Se (unspecified oxidation state) is disclosed to be 0.0042% of that of ZnS (by weight), this does not allow a skilled artisan to determine the aggregation state and the size of the Se contaminant. Accordingly, Labrenz et al. did not disclose Se(0) particles with a diameter of 0.4 to 5 nanometers or 0.4 to 1 nanometer. Therefore, claims 2, 4-6, 8, and 9 are not anticipated by Labrenz et al. further for this reason.

Lastly, Labrenz et al. did not disclose a carrier molecule as recited in claims 2, 8, and 9. Therefore, claims 2, 8, and 9 are not anticipated by Labrenz et al. further for this reason.

2. Rejection based on Lou et al.

With respect to Lou et al., the Examiner asserts that the reference disclosed Lp(a)-coated colloidal selenium and thus anticipates claims 2, 4-6, 8, and 9. Applicants respectfully traverse the rejection.

Lou et al. refer to Devereaux et al. (European Patent Application 4877745) for the preparation of selenium. As provided in Devereaux et al. (copy attached) at page 12, Example 2, section a, the colloid selenium prepared there was precipitated and washed by centrifugation at 5,000 g for 30 minutes. A skilled artisan would appreciate that any particles that can be pelleted by such modest g-force will be at least 2 orders of magnitude larger than the size of the Se(0) particles recited in the claims at issue. Therefore, claims 2, 4-6, 8, and 9 are not anticipated by Lou et al.

3. Allowable subject matter.

The Examiner indicated that claims 26-30 are allowable and claims 7 and 10-12 are also allowable if rewritten in independent form. In this regard, claims 7, 10, and 11 have been rewritten in independent form and claim 12 has been amended to depend on claim 11.

PART II. RESPONSE TO THE REJECTIONS RAISED IN THE OFFICE ACTION OF AUGUST 25, 2005

In the office action mailed August 25, 2005, the Examiner withdrew several objections and rejections raised in the previous office action and indicated that claims 2, 4-12, and 26-30 were allowable. However, the Examiner maintained the rejection against claims 13-17, 25, and 48-51 (now new claims 52-56, 62, and 63-66, respectively) as being indefinite, maintained the rejection against claim 20 (now new claim 57) as being anticipated by Zhang et al. (BioFactors 15:27-38, 2001), raised a new rejection against claims 21-24 (now new claims 58-61, respectively) as being indefinite, and raised a new rejection against claim 25 (now new claim 62) as being obvious over Zhang et al. (BioFactors 15:27-38, 2001) in view of Kuchan et al. (Cancer Res. 52:1091-1095, 1992). The above maintained and new rejections are addressed separately below.

1. Maintained indefiniteness rejection under 35 U.S.C. §112, second paragraph.

The Examiner maintained the rejection against claims 13-17, 25, and 48-51 (now new claims 52-56, 62, and 63-66, respectively) under 35 U.S.C. §112, second paragraph as being indefinite. In particular, the Examiner alleged that it is not clear as to what a sufficient amount is

with respect to claim 13 for killing a cancer cell and with respect to claim 25 for reducing the intracellular glutathione level. Applicants respectfully traverse the rejection.

MPEP §2173.05(c)III provides that the common phrase "an effective amount" may or may not be indefinite and the proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure. The section cites an example (*In re Fredericksen* 213 F.2d 547 (CCPA 1954)) wherein the phrase "an effective amount" was held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. The section also cites an example (*Ex parte Skuballa* 12 USPQ2d 1570 (BD. Pat. App. & Inter. 1989)) wherein although the claim failed to state the function to be achieved, the term "effective amount" was held to be definite because the intended utilities and how the uses could be effected are provided in the supporting disclosure. The section further notes that in general the more recent cases have tended to accept a limitation such as "an effective amount" as being definite when read in light of the supporting disclosure and in the absence of any prior art which would give rise to uncertainty about the scope of the claim.

The term "an amount sufficient" recited in claims 13 and 25 is analogous to the term "an effective amount" discussed in MPEP §2173.05(c)III and claims 13 and 25 clearly recite the functions to be achieved. For claim 13 it is the killing of a cancer cell and for claim 25 it is the reduction of intracellular glutathione level. The specification also provides plenty of supporting examples in this regard. For the use of Se(0) particles to treat cancer, *see, e.g.,* Example 3 and related Fig. 9, Example 4 and related Figs. 13-15 and Table 4, Example 5 and related Table 5, and Example 6 and related Figs. 16-23 and 25-27. For the use of Se(0) particles to reduce intracellular glutathione levels, *see, e.g.,* Example 3 and related Fig. 10 and Example 6 and related Fig. 24. In addition, the Examiner has not presented any prior art that would give rise to uncertainty about the scope of the claims as provided under MPEP §2173.05(c)III.

In a seminal case on the construction of the second paragraph of 35 U.S.C. §112, *In re Borkowski* (422 F.2d 904, 909 (CCPA 1970)), the court observed that "[I]f the scope of subject matter embraced by a claim is clear, and if applicant has not otherwise indicated that he intends that claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention." It is clear from the above-

cited language that what the second paragraph of §112 requires is that the claim language must clearly set out the boundaries of the subject matter being claimed so that one of skilled in the art is able to tell with a reasonable degree of certainty whether his or her conduct is within or outside the scope of the claim. Applicants respectfully submit that when one skilled in art uses Se(0) particles to kill cancer cells or to reduce intracellular glutathione levels, he or she can readily determine what amount is effective and what is not. Therefore, the boundaries of the claims are clear. There will not be any ambiguity as to whether a particular conduct of a skilled artisan is within or outside the scope of the claims at issue.

For the above reasons, applicants respectfully submit that new claims 52-56, 62, and 63-66 (corresponding to claims 13-17, 25, and 48-51, respectively) are definite.

2. Maintained rejections under 35 U.S.C. §102 (b).

The Examiner maintained the rejection against claim 20 (now new claim 57) under 35 U.S.C. §102(b) as being anticipated by *Zhang et al.* (Biofactors 15:27-38, 2001), alleging that *Zhang et al.* teach that Se(0) can protect cells against paraquat-induced cell death (page 32, results 3.2 and Fig. 5) and that the protected cells contain glutathione (GSH). In the Examiner's opinion, Zhang et al. meet the limitations of claim 20 reasoning that the claim does not mention cell death.

New claim 57 corresponds to rejected claim 20. New claim 57 now specifies that treating the cell with Se(0) renders the cell susceptible to the killing by an otherwise ineffective amount of the cytotoxic agent. As already discussed in the response of June 16, 2005, claim 20 (now new claim 57) is directed at using Se(0) to sensitize cells to other cytotoxic agents and as a result promoting the cell killing activity of these other cytotoxic agents. This is the opposite of what Zhang et al. teach, *i.e.*, using Se(0) to protect cells from a cytotoxic agent (e.g., paraquat)-induced cell death. In view of the added clarification in new claim 57, applicants respectfully submit that new claim 57 is not anticipated by Zhang et al.

3. New indefiniteness rejection under 35 U.S.C. §112, second paragraph.

The Examiner rejected claims 21-24 (now new claims 58-61) under 35 U.S.C. §112, second paragraph as being indefinite. In particular, the Examiner alleged that it is not clear how a cytotoxic agent can induce cell death when the cell is resistant to the agent.

New claims 58-61 correspond to rejected claims 21-24, respectively. New claims 58-61 clarify that the cell resistant to the cytotoxic agent will become susceptible to the cytotoxic agent after it is treated with Se(0). In view of the added clarification, applicants respectfully submit that new claims 58-61 are definite.

4. New obviousness rejection.

The Examiner rejected claim 25 (now new claim 62) under 35 U.S.C. §103(a) as being obvious over Zhang et al. (BioFactors 15:27-38, 2001) in view of Kuchan et al. (Cancer Res. 52:1091-1095,1992), alleging that Zhang et al. teach that Se(0) can reduce glutathione levels *in vitro* (cell-free) and Kuchan et al. teach that selenite can reduce the level of intracellular glutathione in cultured cells. In the Examiner's opinion, it would have been obvious to a person having ordinary skill in the art to use Se(0) particles to reduce glutathione levels *in vivo*. Applicants respectfully traverse the rejection in that there is no motivation to combine the two references. In fact, the two references may even teach away from the present invention. The rejection is also traversed in that even assuming for the sake of argument that a skilled artisan would combine the two references, they will only make the present invention obvious to try but without reasonable likelihood of success.

Zhang et al. showed that selenite was 12.3 times more effective than nano-Se in reducing the level of GSH in vitro (see page 32, section 3.4, lines 4 and 5 and Fig. 8). This is consistent with the notion that selenite (Se^{4+}) is a much stronger oxidizing agent than Se(0). Therefore, it would be expected that Se(0) would not work as effectively as selenite, if at all, *in vivo*. Accordingly, if Zhang et al. and Kuchan et al. teach anything, it would be using the more effective selenite rather than the less or potentially not effective Se(0) *in vivo*, especially when Kuchan et al. have shown that selenite works well *in vivo*. At the very least, given that there is already an agent, selenite, that can be used to reduce glutathione levels *in vivo* and Se(0) would be expected to work less well, if at all, there is no motivation or need to combine the two references and try to use Se(0) *in vivo* for reducing glutathione levels.

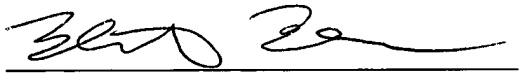
Even for sake of argument that the two references would be combined, the present invention is merely obvious to try but without reasonably likelihood of success. While Zhang et al. showed that both selenite and Se(0) worked *in vitro* and Kuchan et al. showed that selenite worked *in vivo*, one still cannot predict with reasonable certainty that Se(0) would also work *in vivo* because in addition to glutathione, which provided as the only molecule to react with selenium in the *in vitro* system of Zhang et al. (page 29, method 2.4), there are many other types of molecules in a cell that may interact with Se(0) *in vivo*. Therefore, just because the much stronger oxidizing agent selenite reduced glutathione levels *in vivo* does not mean that the much weaker oxidization agent Se(0) would not be titrated out by other types of molecules *in vivo* before being able to react with GSH.

For all the above reasons, it is respectfully submitted that new claim 62 is not obvious over Zhang et al. over Kuchan et al.

PART III. CONCLUSION.

Having addressed each rejection raised by the Examiner in the instant office action as well as the office action mailed August 25, 2005, the currently pending claims are believed to be in condition for allowance and a Notice of Allowance is respectfully requested. Should any issues remain outstanding, the Examiner is invited to contact the undersigned at the telephone number appearing below if such would advance the prosecution of this application.

Respectfully submitted,



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